Synthesis of Diazepam Related Analogues of Miltirone, an Active Central Benzodiazepine Receptor Ligand Isolated from *Salvia miltiorrhiza* Bunge (Danshen)

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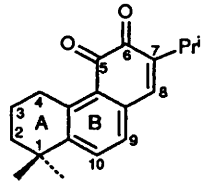
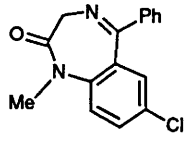
New compounds related to miltirone and diazepam containing a halogen substituent in ring B or a heterocyclic nitrogen atom in ring A have been synthesized.

Of the compounds isolated from the roots of *Salvia miltiorrhiza* Bunge (Danshen),[1] miltirone **1**[2] exhibited the highest potency in the central benzodiazepine receptors assay (0.3 μM).[1] In order both to improve and assess further miltirone's potential tranquilizing activity, we have synthesized new compounds whose structures, **3a–c** and **4a–b**, are structurally related both to miltirone **1** and to diazepam **2**.

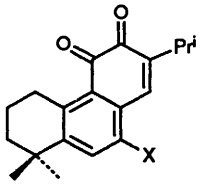
Preliminary experiments to synthesize the halogen-substituted compounds **3a–c** were based on electrophilic substitution[4] of the known compound **5**.[1] Regioselective substitution of a polysubstituted naphthalene, however, is never a trivial reaction (*e.g.* 2-methoxynaphthalene is nitrated at the 1-, 6- and 8-positions).[5] Thus, compound **5**, upon treatment with nitric acid–sulphuric acid, gave a chromatographically separable mixture of 5-nitro-**5** and 10-nitro-**5** (ratio 4:1). In the light of this discouraging result we reasoned that steric hindrance arising from the *gem*-1,1-dimethyl groups, the 6-methoxy group and the 7-isopropyl group might, under conditions of Friedel-Crofts acetylation,[6] enhance stereoselective substitution at the 9-position of **5**. This proved to be so. The 9-acetyl substitution pattern of **6a** † was established by a 2D ^{1}H-^{1}H NOESY study.‡ Deprotection of **6a** with boron tribromide yielded the phenol **6b**, whose 2:1 adduct with benzene has been structurally



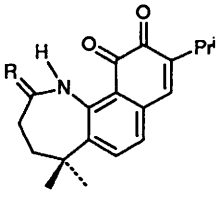
1 Miltirone



2 Diazepam



3a X = F
3b X = Cl
3c X = Br



4a R = O
4b R = H_2

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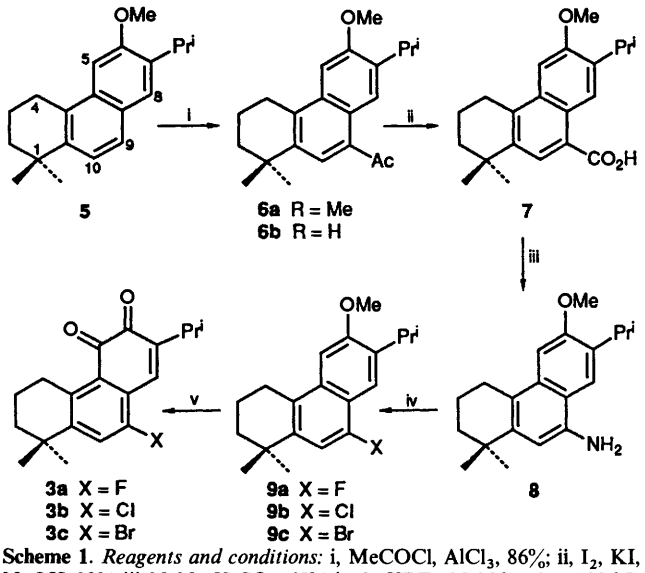
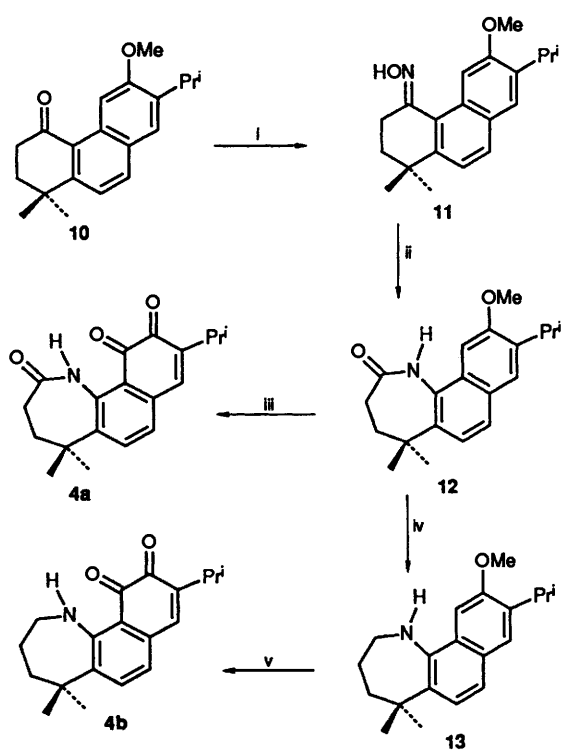
† All new compounds were fully characterized spectroscopically as well as by analytical and/or accurate mass data.

‡ ^{1}H NMR results for compounds **3a**, **3b**, **3c**, **4a**, **4b**, **6a**, **6b**, **7**, **8**, **9a**, **9b**, **9c**, **12** and **13** are available as a supplementary publication [Sup. No. 56799 (19 pp)]. For details of the scheme, see 'Instructions for Authors' (1990), *J. Chem. Soc., Perkin Trans. 1*, 1990, Issue 1.



Scheme 1. *Reagents and conditions:* i, MeCOCl, $AlCl_3$, 86%; ii, I_2, KI, NaOH, 83%; iii, NaN_3, H_2SO_4, 65%; iv, **9a** HBF_4, $NaNO_2$, then 180 °C, 59%; **9b** HCl, $NaNO_2$, then Cu_2Cl_2, 81%; **9c** HBr, $NaNO_2$, then Cu_2Br_2, 26%; v, **3a** BBr_3, CH_2Cl_2, 95%, then $(KSO_3)_2NO$, KH_2PO_4, H_2O, Me_2CO, 48%; **3b** BBr_3, CH_2Cl_2, 94%, then $(PhSeO)_2O$, CH_2Cl_2, 91%; **3c** BBr_3, CH_2Cl_2, 89%, then $(KSO_3)_2NO$, KH_2PO_4, H_2O, Me_2CO, 31%.

characterized by X-ray crystallography (Fig. 1).* With this regiospecific access to **6a**, conversion of the acetyl group into a halogen[7] provided the acid **7**, which smoothly underwent Schmidt rearrangement[8] to afford the amine **8**. The Sandmeyer[9] and Schiemann[10] reactions transformed **8** to **9a**, **9b** and **9c**, respectively. In addition to the 2D NMR spectroscopic evidence, the structure of **9a** has also been unambiguously proved by an X-ray crystallographic study (Fig. 2).‡ Finally, straightforward deprotection and oxidation of the resulting phenols with either potassium nitrosodisulphonate (Fremy's salt)[11] or benzeneseleninic anhydride[12] furnished the target molecules **3a**, **3b** and **3c**, respectively (Scheme 1).†



Scheme 2. *Reagents and conditions:* i, NH_2OH·HCl, C_5H_5N, EtOH, 94%; ii, PPA, CH_2Cl_2, 60–70 °C, 85%; iii, BBr_3, CH_2Cl_2, 73%, then $(PhSeO)_2O$, THF, 70 °C, 81%; iv, $LiAlH_4$, Et_2O, 89%; v, BBr_3, CH_2Cl_2, 75%, then $(PhSeO)_2O$, THF, 70 °C, 80%.

Next we attempted to synthesize the nitrogen heterocycles **4a** and **4b** *via* the oxime **11**, prepared from the known ketone **10**.[1] Beckmann rearrangement[13] effected the conversion of **11** into the amide **12**, which upon reduction provided the amine **13**. Again, deprotection of **12** and **13** and subsequent oxidation of their corresponding phenols with benzeneseleninic anhydride provided the target molecules **4a** and **4b**, respectively (Scheme 2).†

In summary, halogen substituted compounds **3a–c** and their nitrogen heterocyclic analogues **4a–b** have been successfully synthesized. Special mention should be made of the highly efficient regiospecific synthesis of **3a–c**. Of all the new compounds synthesized, only **4b** showed a higher potency (*i.e.* 0.05 μM) in inhibiting the binding of [^{3}H]flunitrazepam to central benzodiazepine receptors.[14]

Experimental

Representative examples of preparations are given below.

9-Acetyl-1,2,3,4-tetrahydro-7-isopropyl-1,1-dimethyl-6-methoxyphenanthrene **6a**.—Aluminium chloride (400 mg, 3 mmol) was mixed with anhydrous 1,2-dichloroethane (2 ml) cooled at 0 °C. Acetyl chloride (300 μl) followed by a solution of **5** (200 mg, 0.7 mmol) in anhydrous 1,2-dichloroethane (2 ml) were then introduced. The bath temperature was allowed to rise from 0 °C to room temperature during 1 h, after which the reaction mixture was stirred at room temperature overnight. It was then decomposed with ice (10 g) and 2M hydrochloric acid (10 ml) and extracted with ethyl acetate (3 × 40 ml). The combined organic extracts were washed with dilute aqueous sodium hydrogen carbonate (2 × 20 ml) and brine (2 × 20 ml), dried

* *Crystal data for the* 2:1 *adduct of* **6b** *with benzene.* Nicolet R3m/V diffractometer using graphite-monochromatized Mo-Kα radiation, λ = 0.710 73 Å; $2(C_{21}H_{26}O_2)\cdot C_6H_6$, M = 699.06, monoclinic, space group $P2_1/a$, a = 9.781(2), b = 17.238(3), c = 12.350(1) Å, β = 92.42(1)°, U = 2080.4(6) Å^3, Z = 2, ρ_{calc} = 1.116 g cm^{-3}, μ = 0.59 cm^{-1}, crystal size 0.28 × 0.32 × 0.40 mm, mean μ_r = 0.010, transmission factors 0.939–1.000, 2θ = 45°, ω-2θ variable-scan technique, 2744 unique reflections. All non-hydrogen atoms were refined anisotropically, and all H atoms were included in structure-factor calculations. Final R_w based on 1584 observed data [$|F_o| > 6\sigma(F_o)$] and 247 parameters is 0.068.

Crystal data for **9a**. Nicolet R3m/V diffractometer using graphite-monochromatized Mo-Kα radiation, λ = 0.710 73 Å; $C_{20}H_{25}FO$, M = 300.45, monoclinic, space group $P2_1/n$, a = 9.684 2(8), b = 15.090(2), c = 11.730(2) Å, β = 96.62(1)°, U = 1 702.7(4) Å^3, Z = 4, ρ_{calc} = 1.172 g cm^{-3}, μ = 0.73 cm^{-1}, crystal size 0.60 × 0.64 × 0.72 mm, mean μ_r = 0.024, transmission factors 0.923–0.944, 2θ = 55°, ω variable-scan technique, 3915 unique reflections. All non-hydrogen atoms except the two-fold disordered C(8) atom [treated as C(8a) and C(8b), each of half site occupancy] were refined anisotropically, and the H atoms of C(8a), C(8b) and C(9) were not included in structure-factor calculations. Final R_w based on 2305 observed data [$|F_o| > 6\sigma(|F_o|)$] and 198 parameters is 0.082.

For both crystals, atomic co-ordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See 'Instructions to Authors (1990),' *J. Chem. Soc., Perkin Trans. 1*, 1990, Issue 1.

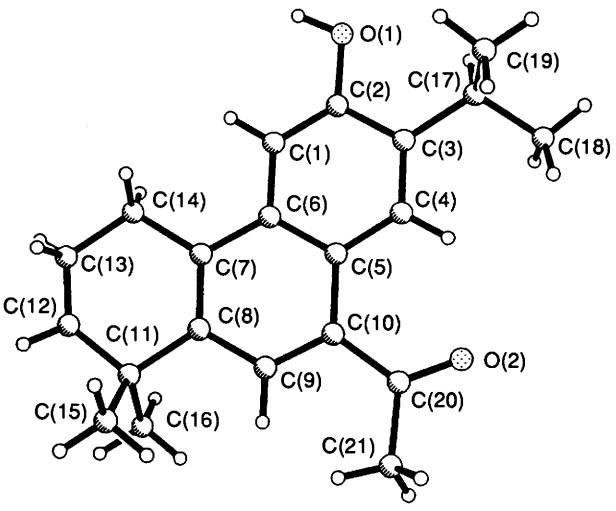


Fig. 1. A perspective view of molecule **6b** as determined in its 2:1 adduct with benzene

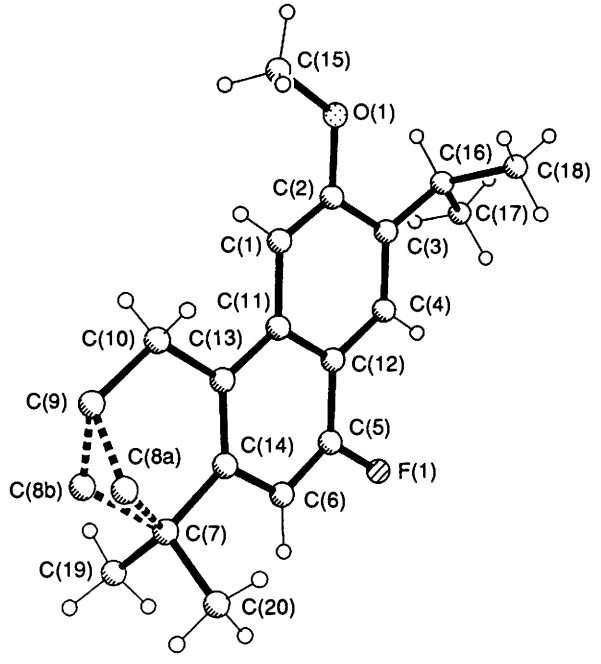


Fig. 2. A perspective view of molecule **9a**. Atom C(8) exhibits two-fold positional disorder

(Na_2SO_4) and evaporated. The residue was chromatographed on a column of silica gel (230–400 mesh, 10 g, hexanes–ethyl acetate, 95:5) to afford **6a** (185 mg, 86%) as colourless needles (from chloroform–hexanes), m.p. 105.5–106.5 °C (Found: C, 81.05; H, 8.8. $C_{22}H_{28}O_2$ requires C, 81.48; H, 8.64%); δ(250 MHz, $CDCl_3$) 8.60 (1 H, s), 7.81 (1 H, s), 7.20 (1 H, s), 3.94 (3 H, s), 3.48 (1 H, septet, *J*/Hz: 6.4), 3.06 (2 H, t, *J*/Hz: 6.4), 2.75 (3 H, s), 1.96 (2 H, m), 1.72 (2 H, m), 1.36 (6 H, s) and 1.31 (6 H, d, *J*/Hz: 6.8); *m/z* 324 (M^+).

2,3,4,5-Tetrahydro-9-isopropyl-10-methoxynaphtho[6,5-f]-*azepin-2-one* **12**.—A solution of the oxime **11** (1 g, 3.4 mmol) in methylene dichloride (20 ml) was added dropwise to stirred polyphosphoric acid (20 g) heated at 70–75 °C. The reaction mixture was then stirred for 30 min after which it was poured into ice–water (100 ml). The resulting mixture was extracted with ether (3 × 150 ml) and the combined ethereal extracts, were dried (Na_2SO_4) and evaporated. The residue was chromatographed on a silica gel column (230–400 mesh, 150 g, hexanes–ethyl acetate, 70:30) to give **12** (0.9 g, 85%) as light yellowish crystals (from hexanes–ethyl acetate), m.p. 208–210 °C (Found: C, 76.7; H, 8.15; N, 4.25. $C_{20}H_{25}NO_2$ requires C, 77.14; H, 8.09; N, 4.50%); δ 8.18 (1 H, s), 7.61 (1 H, s), 7.43–7.63 (2 H, ABq, *J*/Hz: 8.2), 7.21 (1 H, s), 3.98 (3 H, s), 3.41 (1 H, septet, *J*/Hz: 6.8), 2.31 (4 H, m), 1.50 (6 H, s), 1.30 (6 H, d, *J*/Hz: 6.9); *m/z* 311 (M^+).

Acknowledgements

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